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How chronic is polypharmacy in old age? A longitudinal nationwide cohort study

Running title: The chronicity of polypharmacy

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Impact statement:
We certify that this novel clinical investigation provides original research about the chronicity of polypharmacy in a large and unselected cohort of older adults. A deeper understanding of the dynamic nature of polypharmacy is an important addition to the current literature.

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Abstract

OBJECTIVE: To evaluate the chronicity of polypharmacy among older adults, and to identify factors associated with chronic polypharmacy.

DESIGN: Longitudinal cohort study using register data.

SETTING: Nationwide, Sweden.

PARTICIPANTS: All 711,432 older adults (≥65 years) living in Sweden with 5 or more prescription drugs in October 2010 were included and followed-up until December 2013. Mean age at baseline was 77 (SD, 7.8) years, 59% were women, and 7% lived in nursing homes.

MEASUREMENT: Monthly changes in the exposure to polypharmacy. Data regarding prescription drug use were extracted from the Swedish Prescribed Drugs Register.

RESULTS: Overall, 82% were continuously exposed to polypharmacy during ≥6 months, and 74% during ≥12 months. The proportion of individuals who remained exposed until the end of the study was 55%. Among the 21,361 individuals who had not been exposed to polypharmacy during the 6-month period before baseline (i.e. with a new episode of polypharmacy), only 30% remained exposed for ≥6 months. The proportion of older adults who spent at least 80% of their follow-up time with polypharmacy was substantially higher among prevalent polypharmacy users at baseline than among those with a new polypharmacy episode (80% vs 24%, $p<0.01$). Factors associated with chronic polypharmacy included higher age, female gender, living in an institution, chronic multimorbidity, and multi-dose dispensing.

CONCLUSION: Polypharmacy is most often chronic, although a substantial share of older adults experience short, recurring episodes of polypharmacy and are thus exposed to its potential harms in a transient rather than persistent manner.

Keywords: duration; drugs; epidemiology; medication; polypharmacy

Introduction

Multimorbidity is common among older adults and often results in multiple medication use. Polypharmacy (commonly defined as the concurrent use of 5 or more drugs)[1] is a concern because it has been linked to an array of negative health outcomes.[2–6] The prevalence of polypharmacy has increased in most countries during the last decades [7–11]. In the United States, it is estimated that about 40% of people aged 65 years or older use ≥5 drugs concomitantly.[7] Yet few studies have documented the longitudinal development of polypharmacy over time, and little is known about the proportion of older adults who are chronically exposed to polypharmacy. Prior studies suggest that older adults tend to persist with polypharmacy over time.[12–16] Factors such as higher age, female gender, high BMI, smoking and chronic conditions are associated with higher odds of remaining on polypharmacy.[16] However, these studies were based on survey data with several years between each wave. The use of prescription drugs by older adults can fluctuate, and episodes of polypharmacy can occur sporadically. Newly diagnosed chronic conditions and temporary changes in health status (e.g. post-operative pain, infections) can for instance prompt an increase in the number of drugs, while deprescribing and lack of adherence can shorten the medication list.

Understanding the chronicity of polypharmacy is important for a number of reasons[17]. First, most definitions of polypharmacy do not consider whether the exposure to polypharmacy is chronic or transient.[18,19] Yet, this has implications for evaluating the quality of drug prescribing since short-term exposure to polypharmacy as a response to acute events is often clinically appropriate. Second, various interventions have been implemented to reduce the

prevalence and the harms of polypharmacy. Most of these interventions have proven unsuccessful.[20,21] Potentially because polypharmacy may not always be a chronic and persistent hazard,[22] making it difficult to provide tailored interventions at the right time for older adults[18]. Third, observational studies aiming at establishing a causal association between polypharmacy and subsequent health outcomes have seldom considered polypharmacy as a time-varying or cumulative exposure based on the assumption that polypharmacy is by definition chronic.[23] Yet, until now, this assumption has remained untested and there exists no consensual definition of what constitutes *chronic polypharmacy.*[19] Our aim was thus twofold: i) to evaluate the degree of chronicity of polypharmacy among older adults in Sweden, and ii) to identify factors associated with chronic rather than transient polypharmacy.

Methods

Study population

We used register data with nationwide coverage in Sweden to create a longitudinal cohort of older adult (≥65 years) who were exposed to ≥5 drugs in October 2010. Study participants were followed prospectively until December 2013, i.e. for up to 37 months. The Swedish Prescribed Drug Register was linked to the National Patient Register, the National Cause of Death Register, and the Social Services Register, as described elsewhere.[24] We excluded individuals who died during the first 12 months of follow-up, as people at the end of life might have specific clinical needs.[25] The selection of the study population is presented in Supplementary materials Figure S1.

Outcome measurement: polypharmacy

Data regarding prescription drug use were extracted from the Swedish Prescribed Drugs Register, which collects information about all prescription drugs delivered in pharmacies in Sweden.[26] Exposure periods were constructed for each dispensed drug based on: (i) the date of drug dispensing, (ii) the number of dispensed defined daily doses, and (iii) the prescribed daily dose as reported by the prescriber.[27,28] We then calculated the number of different drugs used in each 30-day window, i.e. distinct substances according to the 5th level of Anatomical Therapeutic Chemical (ATC) classification system. As illustrated in Figure S2, individuals were considered as exposed to polypharmacy during a given month when the number of drugs was ≥5.

To distinguish "chronic" from "transient" polypharmacy exposure, we used the different approaches illustrated in Figure 1. Health problems are usually defined as "chronic" when they persist over time without any measurable interruptions (e.g. diabetes, heart failure). To reflect this, we calculated the *duration* of polypharmacy as the number of consecutive months spent with ≥5 different drugs. We considered the first episode, starting at baseline and stopping when the patient was no longer exposed to polypharmacy for at least 2 months. In other words, interruptions in polypharmacy exposure were discarded if they lasted ≤1 month. This 'grace period' was used to reduce the influence of irregular drug refill patterns. Chronicity of polypharmacy was calculated as the proportion of individuals who remained exposed for ≥6 months and ≥12 months.

Other health problems do not persist over time without any measurable interruption, but can still be considered as chronic if people are experiencing them more often than not (e.g. chronic pain, psoriasis). The underlying assumption is that some conditions occur so frequently that their impact on people's everyday life is constant although their onset appears as a series of discrete events. In order to mirror this second scenario, we calculated the *fraction of time with polypharmacy* by dividing the number of months with polypharmacy (numerator) by the total number of months of available follow-up (denominator). The numerator did include grace periods. We then defined chronic polypharmacy users as older adults who had a fraction of time with polypharmacy ≥80% (e.g. at least 30 months out of 37 for those surviving the complete follow-up). This is similar to how drug adherence is calculated using the medication possession ratio.[29]

[Figure 1 about here]

Other covariates

Living arrangement at baseline was defined as 'community-dwelling' or 'living in institution', using data from the Social Services Register. *Multimorbidity* was assessed using a validated assessment tool (5), which captures 60 distinct chronic diseases using data from the national patient register during the 3 years prior to baseline, as well as data about specific medications dispensed during the same period. This variable was defined as the number of chronic conditions, with ≥5 conditions as the maximum value. *Multi-dose dispensing* (in Swedish, *ApoDos*) refers to drugs administered through portion packed plastic pouches. It is especially common among older adults living in nursing homes in Sweden.[30]

Statistical analysis

We calculated the duration of polypharmacy for each individual, and identified those who remained exposed for ≥ 6 and ≥12 consecutive months. To account for left censoring we stratified the population according to their exposure to polypharmacy during the 6-month period *before* baseline. Since we excluded older adults who died during the first year of follow-up, outcome measurement was not affected by right censoring (i.e. survival). However, the persistence of polypharmacy throughout the entire follow-up was analyzed with Kaplan-Meier survival functions accounting for mortality. We then measured the fraction of time with polypharmacy as the number of months spent with polypharmacy divided by the total number of months of available follow-up. The proportion of older adults who had a fraction of time with polypharmacy ≥80% was reported with percentages. Since this indicator is proportional to the contributing time of each individual, it is not affected by mortality selection. We analyzed factors associated with a high fraction of time with

polypharmacy using multivariate logistic regression models adjusted for age, sex, living arrangement, number of chronic conditions, dispensing regimen and number of drugs at baseline. All estimates from the logistic regression are calculated as predicted probabilities and presented as percentages (with 95% confidence intervals) using the margins command in Stata version 14.1 (StataCorp, College Station, TX). Predicted probabilities can be compared across models and can be interpreted as adjusted proportions conditional on the covariates.[31] Post hoc, we stratified the analysis by dispensing regimen to investigate the combined effect of living arrangement and dispensing regimen. In sensitivity analyses, the fraction of time with polypharmacy was categorized using a lower cut-off value (50% instead of 80%), which has previously been used as a definition of chronic polypharmacy [32]

Ethical approval

Data were anonymized and the Regional Ethical Review Board in Stockholm approved the study (2013/1941-31/3 and 2015/1319-32).

Results

Out of 1,752,022 older adults (≥65 years) alive at baseline, 769,286 were exposed to polypharmacy. After excluding 57,854 individuals who died during the first 12 months of follow-up, the study population thus consisted of 711,432 older adults (Supplementary Figure S1). This represents 44% of the population aged ≥65 years in Sweden. Mean age at baseline was 77.4 years (SD 7.8), 59.1% were women. About 3% (n=21,361) of study participants started a new episode of polypharmacy, i.e. had not been exposed to polypharmacy during the 6-month period before baseline (Table 1). Persons with a new episode of polypharmacy were on average younger, had fewer chronic conditions and used fewer drugs at baseline (Table S1).

[Table 1]

Polypharmacy was often long lasting. Overall, 82.3% of participants were exposed to polypharmacy for ≥6 months, and 74.3% for ≥12 months. Among older adults with a new polypharmacy episode, these proportions were 29.8%, and 18.6%, respectively (Table 2). The proportion of individuals who remained exposed to polypharmacy until the end of follow-up was 55.3% in the total study population, but only 9.3% among people who had not been exposed to polypharmacy before baseline. Among the 317,478 older adults who discontinued polypharmacy, 76.3% experienced at least one more episode of polypharmacy during the follow-up period (Table S2). As shown in Figure 2, polypharmacy persisted for a longer time among older adults aged 75 or older than among younger individuals. Episodes of polypharmacy were also longer among individuals with a higher number of medications at baseline (Figure S3).

[Table 2]

[Figure 2]

During follow-up, we observed 21.2 million person-months with polypharmacy out of a total of 25.3 million person-months of follow-up. The average fraction of time with polypharmacy was thus 84%, ranging from 80% among individuals aged 65–74 years to 89% among those aged 95 years and older. Table 3 shows the proportion of older adults with a high fraction of time with polypharmacy, i.e. exposed to polypharmacy for ≥ 80% of follow-up. In the total study population, 79.9% of older adults had a high fraction of time with polypharmacy, compared with 23.6% among persons with a new polypharmacy episode at baseline. After adjustment for potential confounders, this proportion increased with age, as well as with multi-dose drug dispensing compared with ordinary prescriptions (adjusted predicted probability 93% vs 78%, $p<0.01$). The proportion of nursing home residents with a high fraction of time with polypharmacy was higher than among community dwellers (90.7% vs 79.1%). However, after adjustment for other covariates, this association was reversed (predicted probability 76.7% vs. 80.1%). In post-hoc analysis, we explored the interaction between living arrangement and drug dispensing scheme. This showed that community-dwellers with multi-dose dispensing were in fact more likely to have a high fraction of time with polypharmacy than persons living in institution (Table S3). In sensitivity analyses where the fraction of time with polypharmacy was calculated without the one month grace period which yielded similar numbers, and using a cut-off value of ≥50% which left the association with other covariates largely unaffected although a larger proportion of older adults were classified as chronic polypharmacy users (Table S4 and S5).

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Discussion

This large longitudinal cohort study tracking monthly changes in drug utilization among older adults in Sweden shows that polypharmacy (concurrent use of ≥5 drugs) is often a chronic state. This was demonstrated with two complementary approaches.

First, when focusing on the *duration* of polypharmacy episodes, our data clearly show that polypharmacy is persistent for a majority of older adults. About 75% of the individuals with polypharmacy at baseline remained exposed to polypharmacy for at least 12 consecutive months. Moreover, even though persons with a new polypharmacy episode at baseline were more likely to discontinue polypharmacy in the short term, more than three quarters of the people who stopped polypharmacy eventually transitioned back to polypharmacy before the end of the study period. This suggests that polypharmacy is often a chronic state, however a substantial share of older adults experience short episodes of polypharmacy and are thus exposed to its potential harms in a transient rather than persistent manner. This is especially true among those who are prescribed 3 to 4 medications for the management of chronic diseases (and who are likely to fluctuate around the threshold of 5 drugs used to define polypharmacy).

Another way to assess the longitudinal exposure to polypharmacy is to investigate the proportion of months that older adults spend with polypharmacy. Contrary to *duration*, which measures the length of continuous and uninterrupted polypharmacy episodes and is therefore particularly sensitive to grace periods and right censoring (e.g. survival), the *fraction of time with polypharmacy* describes the burden of polypharmacy with respect to the available follow-up time. This approach is comparable to the methodology proposed by Franchi et al.,

for defining chronic polypharmacy users, which consists in measuring the proportion of individuals exposed to polypharmacy at least 6 out of 12 months.[32] In the present study, we found that 80% of older adults had a high *fraction of time with polypharmacy* (i.e. spent ≥80% of follow-up with polypharmacy), which is indicative of a chronic exposure. Risk factors associated with high fraction of time with polypharmacy included higher age, female gender, living in institution, chronic multimorbidity, and multi-dose dispensing [33–35]. When using the same cut-off value as Franchi et al.[32] – namely being exposed to polypharmacy during more than 50% of the available months – 42% of older adults who started a new polypharmacy episode at baseline had chronic polypharmacy in our study. An unexpected finding was that the adjusted probability of spending a large proportion of months with polypharmacy was higher among people residing in the community than in nursing homes. However, more detailed analyses revealed that this association was mostly driven by multi-dose dispensing – the small share of persons living in the community with multi-dose drug dispensing had the largest fraction of time with polypharmacy. The finding that people with multi-dose dispensing spend a higher fraction of time with polypharmacy is in agreement with previous Swedish studies showing that persons with multi-dose dispensing have fewer changes made to their drug regimens (e.g. dose adjustments, drug discontinuations and newly prescribed drugs) [3036]. One suggested reason for the fewer changes is that prescribers have the possibility to renew all drugs at once, which is not possible with ordinary prescriptions [36].

There currently exists no consensual definition of polypharmacy, but two aspects have been widely discussed: the number of drugs that defines polypharmacy in a clinically meaningful way,[37,38] and the criteria that would allow for drawing the line between appropriate and inappropriate polypharmacy.[20] These two dimensions – the *intensity* and the *composition* of

polypharmacy – are indeed important. However, only few studies have made a distinction between chronic and transient polypharmacy.[19] Our study shows that exposure to polypharmacy is not always stable over time, and that transient polypharmacy episodes are not uncommon. The notion of *temporality* should thus be better accounted for in the future. Observational studies that have investigated the association between polypharmacy and negative health outcomes have seldom considered polypharmacy as a time-varying exposure.[2,39] Yet, doing so would considerably improve the assessment of harms of polypharmacy and could potentially elucidate the question whether the effect of polypharmacy is cumulative (i.e. longer exposure to polypharmacy leads to an accumulated risk of adverse effects) or if polypharmacy is hazardous even if exposure is short-lasting. The potential cumulative hazard of polypharmacy was recently highlighted in a British study, which demonstrated that the associations between polypharmacy and physical and cognitive capabilities was more pronounced among older adults with a long-term exposure to polypharmacy.[23]

Strengths and limitations

The main strength of this study is that it includes the entire population of older adults aged ≥65 years with polypharmacy in Sweden, followed up for 3 years. The monthly assessments of polypharmacy exposure provides better time resolution of the fluctuations in polypharmacy status than earlier survey-based studies with longer time periods between survey waves.[12–16,23] There are some notable limitations to the study. First, we assessed monthly exposure to polypharmacy rather than weekly or even daily exposure periods, which could overlook some of the fluctuations in drug use. The choice of monthly time windows was dictated by the considerable computation power required to calculate concurrent drug

exposure for a population of 700,000 individuals over 3 years with a more detailed time resolution. It should also be noted that drugs used in hospitals are not recorded in the Swedish Prescribed Drug Register, and a one-month stay in hospital could thus result in a change in polypharmacy because of not filling new prescriptions. Additionally, over the counter drugs are not recorded in the Swedish Prescribed Drug Register, this most likely leads to an underestimation of the individual burden of polypharmacy. Adherence to different medications could lead to misclassification of the exposure to polypharmacy in this study: our data do not provide information about drugs that were prescribed but never dispensed or whether the dispensed drugs were actually consumed. Our results should be interpreted in the light of this limitation. To reduce the risk of overestimating short-term fluctuations, we only considered polypharmacy to be discontinued if two consecutive months were spent without polypharmacy. Second, we calculated the number of drugs by summing together all distinct ATC codes including medications intended for short-term use that do not contribute to chronic polypharmacy. However, considering all prescribed drugs reflects the natural course of polypharmacy in the older population. Fourth, we tried to isolate people with a new episode of polypharmacy at baseline from those who had already been exposed. This is because incident polypharmacy users have been proposed as a promising target for future interventions.[23] However, because we could only construct a 6-month *washout* period before baseline, we cannot be certain that these individuals have a truly incident episode of polypharmacy. Last, polypharmacy is often a result of multimorbidity. We were able to account for the number of chronic conditions at baseline. However, future studies should also investigate how severity of different conditions affects chronicity of polypharmacy.

In conclusion, in this longitudinal study of more than half a million older people followed for up to three years, we found that that about 75% of the persons with polypharmacy were exposed to polypharmacy for at least 12 consecutive months. A large majority of older adult was also exposed to polypharmacy for more than 80% of the total study months. Our results therefore suggest that polypharmacy is most often chronic, but that a substantial share of older adults experience short, recurring episodes of polypharmacy and are thus exposed to its potential harms in a transient rather than persistent manner. This highlights the need to consider polypharmacy as a dynamic state in both epidemiological studies and in clinical practice.

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Elements of Financial/Personal Conflicts	*Author 1 JWW		Author 2 LM		Author 3 MLL		Author 4 KJ	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds		X		X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

References

1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:230.

2. Fried T, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014;62:2261:2261-2272.

3. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5:345-351.

4. Leelakanok N, Holcombe AL, Lund BC, Gu X, Schweizer ML. Association between polypharmacy and death: A systematic review and meta-analysis. J Am Pharm Assoc. 2017;57:729-738.e10.

5. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57-65.

6. George C, Verghese J. Polypharmacy and Gait Performance in Community-dwelling Older Adults. J Am Geriatr Soc. 2017;65:2082-2087.

7. Charlesworth CJ, Smit E, Lee DSH, Alramadhan F, Odden MC. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988-2010. J Gerontol A Biol Sci Med Sci. 2015;70:989-995.

8. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med. 2016;176:473.

9. Wastesson JW, Fastbom J, Johnell K. Expanding the Proportion of Life With Polypharmacy in Sweden : 2006-2013. J Am Med Dir Assoc. 2016;17:957-958.

10. Guthrie B, Makubate B, Hernandez-Santiago V, Dreishculte T. The rising tide of polypharmacy and drug-drug interactions:population database analysis 1995-2010. BMC Med. 2015;13:1-10.

11. Nishtala PS, Salahudeen MS. Temporal Trends in Polypharmacy and Hyperpolypharmacy in Older New Zealanders over a 9-Year Period: 2005-2013. Gerontology. 2014;61:195-202.

12. Wastesson JW, Oksuzyan A, Hjelmborg J, Christensen K. Changes in drug use and polypharmacy after the age of 90: A longitudinal study of the Danish 1905 cohort. J Am Geriatr Soc. 2017;65:160-164.

13. Wastesson JW, Rasmussen L, Oksuzyan A, et al. Drug use among complete responders, partial responders and non-responders in a longitudinal survey of nonagenarians: Analysis of prescription register data. Pharmacoepidemiol Drug Saf. 2017;26:152-161.

14. Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. Fam Pract. 2000;17:261-267.

15. Jyrkkä J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+ Study. Eur J Clin Pharmacol. 2006;62:151-158.

16. Abolhassani N, Castioni J, Marques-Vidal P, Vollenweider P, Waeber G. Determinants of change in polypharmacy status in Switzerland: the population-based

CoLaus study. Eur J Clin Pharmacol. 2017;73:1187-1194.

17. Tan ECK, Sluggett JK, Johnell K, et al. Research Priorities for Optimizing Geriatric Pharmacotherapy: An International Consensus. J Am Med Dir Assoc. 2018;19:193-199.

18. Sirois C, Tannenbaum C, Gagnon M-E, Milhomme D, Émond V. Monitoring polypharmacy at the population level entails complex decisions: results of a survey of experts in geriatrics and pharmacotherapy. Drugs Ther Perspect. 2016;32:257-264.

19. Wang Y-J, Chiang S-C, Lee P-C, et al. Is Excessive Polypharmacy a Transient or Persistent Phenomenon? A Nationwide Cohort Study in Taiwan. Front Pharmacol. 2018;9:120.

20. Patterson SM, Cadogan CA, Kerse N, et al. Interventions to improve the appropriate use of polypharmacy for older people. Hughes C, ed. Cochrane database Syst Rev. 2014;10:CD008165.

21. Johansson T, Abuzahra ME, Keller S, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82:532-548.

22. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014;77:1073-1082.

23. Rawle MJ, Cooper R, Kuh D, Richards M. Associations Between Polypharmacy and Cognitive and Physical Capability: A British Birth Cohort Study. J Am Geriatr Soc. 2018;66:916-923.

24. Morin L, Johnell K, Laroche M-L, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clin Epidemiol. 2018;10:289—298.

25. Morin L, Vetrano DL, Rizzuto D, et al. Choosing Wisely? Measuring the Burden of Medications in Older Adults near the End of Life: Nationwide, Longitudinal Cohort Study. Am J Med. 2017;130:927-936.e9.

26. Wettermark B, Hammar N, MichaelFored C, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16:726-735.

27. Wastesson JW, Parker MG, Fastbom J, Thorslund M, Johnell K. Drug use in centenarians compared with nonagenarians and octogenarians in Sweden: A nationwide register-based study. Age Ageing. 2012;41:218-224.

28. Johnell K, Fastbom J. Comparison of prescription drug use between community-dwelling and institutionalized elderly in Sweden. Drugs Aging. 2012;29:751-758.

29. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing Terminology and Definitions of Medication Adherence and Persistence in Research Employing Electronic Databases. Med Care. 2013;51:S11-S21.

30. Wallerstedt SM, Fastbom J, Johnell K, et al. Drug Treatment in Older People before and after the Transition to a Multi-Dose Drug Dispensing System–A Longitudinal Analysis. Quintas LEM, ed. PLoS One. 2013;8:e67088.

31. Mood C. Logistic regression: Why we cannot do what we think we can do, and what we can do about it. Eur Sociol Rev. 2010;26:67-82.

32. Franchi C, Marcucci M, Mannucci PM, et al. Changes in clinical outcomes for community-dwelling older people exposed to incident chronic polypharmacy: A comparison between 2001 and 2009. Pharmacoepidemiol Drug Saf. 2016;25:204-211.

33. Moen J, Antonov K, Larsson CA, et al. Factors associated with multiple medication use in different age groups. Ann Pharmacother. 2009;43:1978-1985.

34. Hovstadius B, Petersson G. Factors Leading to Excessive Polypharmacy. Clin Geriatr Med. 2012;28:159-172.

35. Jokanovic N, Tan ECK, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and Factors Associated With Polypharmacy in Long-Term Care Facilities: A Systematic Review. J Am Med Dir Assoc. 2015;16:535.e1-535.e12.

36. Sjöberg C, Ohlsson H, Wallerstedt SM. Association between multi-dose drug dispensing and drug treatment changes. Eur J Clin Pharmacol. 2012;68:1095-1101.

37. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012;65:989-995.

38. Langeard A, Pothier K, Morello R, et al. Polypharmacy Cut-Off for Gait and Cognitive Impairments. Front Pharmacol. 2016;7:296.

39. Schöttker B, Saum KU, Muhlack DC, et al. Polypharmacy and mortality: new insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. Eur J Clin Pharmacol. 2017;73:1041-1048.

313 **Supplementary material**

314 Brief title: Supplementary analyses of chronicity of polypharmacy

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Figure captions

Figure 1. Fictitious example of two persons followed from baseline until the end of the study period, i.e. for a follow-up time of 37 months in total. Each square represents 1 month. The washout period of 6 months before baseline is used to distinguish persons who were already exposed to polypharmacy before baseline (Person A) from those who started a new polypharmacy episode at baseline (Person B). Each episode of polypharmacy starts at the first month of exposure, and ends when the person remains unexposed for at least 2 consecutive months (grace period). In this example, both persons are considered as having a first episode of polypharmacy that persisted for 7 months, followed by 2 other episodes of polypharmacy. The fraction of time with polypharmacy is calculated as the number of months with polypharmacy – including grace periods – divided by the total number of months of available follow-up. In this example, the fraction of time with polypharmacy is equal to 33÷37 (89.2%). Thus, considering a cut-off value of ≥80%, these persons are defined as chronic polypharmacy users.

Figure 2: Kaplan-Meier survival functions. Solid-line curves denotes the persistence of polypharmacy with a 2-month grace period. Dotted-line curves denotes the persistence of polypharmacy with no grace period (sensitivity analysis). Vertical dashed lines indicate polypharmacy exposure at 6 and 12 months, respectively.

313 **Table 1.** Characteristics of older adults with polypharmacy at baseline (Sweden, 2010)

Sex, No (%)	
Men	291,175 (40.9%)
Women	420,257 (59.1%)
Age	
Mean (SD)	77.4 (7.8)
No (%)	
65-74 years	300,810 (42.3%)
75-84 years	273,069 (38.4%)
85-94 years	129,715 (18.2%)
95 years +	7,838 (1.1%)
Living arrangement, No (%)	
Community	658,693 (92.6%)
Institution	52,739 (7.4%)
Number of chronic conditions	
Mean (SD)	3.7 (2.6)
No (%)	
0	41,256 (5.8%)
1	102,904 (14.5%)
2	122,735 (17.2%)
3	116,609 (16.4%)
4	98,338 (13.8%)
≥5	229,590 (32.3%)
Drug dispensing scheme, No (%)	
Ordinary prescription	611,123 (85.9%)
Multi-dose dispensing	100,309 (14.1%)
Number of drugs at baseline	
Mean (SD)	8.0 (3.1)
No (%)	
5	149,247 (21.0%)
6	128,527 (18.1%)
7	105,530 (14.8%)
8	83,972 (11.8%)
9	65,710 (9.2%)
≥10	178,446 (25.1%)
Polypharmacy during the 6-month period before baseline, No (%)	
No	21,361 (3.0%)
Yes	690,071 (97.0%)
Death during follow-up, No (%)	

Between 12 and 24 months	54,476 (7.7%)
Between 25 and 37 months	57,027 (8.0%)
Survived follow-up	599,792 (84.3%)

Table 2. Persistence of polypharmacy (≥5 drugs) among older adults in Sweden.

	Entire cohort (n=711,432)		Older adults with a new polypharmacy episode at baseline (n=21,361)	
	≥ 6 months	≥12 months	≥ 6 months	≥12 months
	%	%	%	%
Total	82.3	74.3	29.8	18.6
Sex				
Men	81.8	73.2	31.9	19.9
Women	82.7	75.0	28.2	17.6
Age				
65-74 years	78.1	68.5	26.8	15.6
75-84 years	84.2	76.7	33.0	21.6
85-94 years	87.8	82.0	36.5	25.6
95 years +	88.6	83.2	29.5	17.0
Living arrangement				
Community	81.4	73.0	29.4	18.1
Institution	93.7	90.5	48.4	37.9
Number of chronic conditions				
0	65.2	53.3	20.5	11.5
1	73.2	62.4	25.2	14.7
2	77.4	67.7	29.9	18.2
3	81.2	72.2	34.0	21.7
4	84.8	77.0	36.3	24.2
≥5	91.7	86.7	44.1	31.5
Drug dispensing scheme				
Ordinary prescription	80.2	71.2	29.1	17.8
Multi-dose dispensing	95.5	93.0	51.4	41.8
Number of drugs at baseline				
5	55.0	41.8	23.4	13.7
6	76.1	64.3	35.1	21.5
7	86.7	77.7	46.5	31.2
8	92.0	85.4	56.2	40.3
9	95.0	90.2	69.1	56.6
≥10	97.8	95.5	78.4	67.3
Death during follow-up				
Between 12 and 24 months	90.5	85.9	43.8	34.6
Between 25 and 37 months	89.4	84.4	41.6	29.8
Survived follow-up	80.9	72.3	28.6	17.4

[a] Duration of polypharmacy was calculated as the number of consecutive months with polypharmacy, with a 2-month grace period (see *methods* for more information) .

Table 3. Proportion of older adults with a high fraction of time with polypharmacy (≥80%) during follow-up

	Entire cohort (n=711,432)			Older adults with a new polypharmacy episode at baseline (n=21,361		
	Crude %	Adjusted %[a]	95% CI	Crude %	Adjusted %[a]	95% CI
Total	79.9	79.9	(79.8-80.0)	23.6	23.6	(23.1-24.2)
Sex						
Men	79.3	80.5	(80.4-80.6)	24.5	24.4	(23.6-25.2)
Women	80.0	79.5	(79.4-79.6)	22.9	23.0	(22.3-23.7)
Age						
65-74 years	74.8	77.7	(77.6-77.8)	19.5	20.5	(19.8-21.2)
75-84 years	82.5	81.6	(81.5-81.7)	27.8	27.1	(26.1-28.1)
85-94 years	86.1	82.7	(82.5-82.9)	33.2	29.4	(27.5-31.2)
95 years +	85.9	81.1	(80.2-82.0)	31.0	22.3	(15.7-28.8)
Living arrangement						
Community	79.1	80.1	(80.0-80.2)	23.1	23.4	(22.9-24.0)
Institution	90.7	76.7	(76.1-77.3)	47.2	29.4	(25.1-33.7)
Number of chronic conditions						
0	60.6	75.5	(75.2-75.8)	15.3	17.4	(16.1-18.7)
1	69.5	78.0	(77.8-78.2)	18.7	20.1	(19.0-21.1)
2	74.4	78.7	(78.5-78.9)	23.8	24.1	(22.9-25.2)
3	78.5	79.6	(79.4-79.8)	27.1	26.0	(24.6-27.4)
4	82.8	81.1	(80.9-81.4)	30.8	28.5	(26.6-30.4)
≥5	90.5	84.1	(83.9-84.3)	37.5	31.8	(29.8-33.8)
Drug dispensing scheme						
Ordinary prescription	77.8	79.1	(79.0-79.2)	22.7	23.0	(22.4-23.6)
Multi-dose	92.8	87.9	(87.6-88.2)	50.6	39.9	(35.7-44.1)
Number of drugs at baseline						
5	51.6	55.8	(55.6-56.1)	19.1	19.5	(18.9-20.2)
6	72.1	74.1	(73.8-74.3)	26.7	26.4	(25.1-27.6)
7	83.7	84.2	(84.0-84.4)	35.2	34.2	(32.0-36.5)
8	90.1	89.8	(89.6-90.0)	41.2	38.0	(34.4-41.6)
9	93.8	93.3	(93.1-93.5)	61.4	55.3	(49.6-61.0)
≥10	97.2	96.6	(96.5-96.7)	63.3	56.5	(49.4-63.5)

[a] Probabilities mutually adjusted for the other covariates in the table.